DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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WARNING LETTER

SEP 10 1999

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

Federal Express

Ms. Betty Castor
President
University of South Florida
4202 East Fowler Avenue
Administration Building, Room 241
Tampa, Florida 33620

Dear Ms. Castor:

During the period of May 13-21, 1999, Mr. Ernest A. Clausnitzer, an investigator with the Food and Drug Administration's (FDA) Florida District Office, inspected the University of South Florida's (USF) nonclinical laboratory. The purpose of the inspection was to determine if nonclinical laboratory studies conducted at USF that support or are intended to support device applications for research and marketing were conducted in compliance with applicable FDA regulations. The inspection focused on the "[redacted])" studies. Holmium Lasers are devices as that term is defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The [redacted] studies were processed by USF as three separate studies: Study 1087 entitled, "[redacted]," Dr. P.P. McKeown is recognized as the principal investigator; **Study** 1166 entitled, "[redacted]," Dr. William W. Angell is recognized as the principal investigator; and Study 1167 entitled, "[redacted]" – Training Course, Dr. William W. Angell is recognized as the principal investigator.

Our review of the inspection report submitted by the Florida District Office revealed serious violations of Title 21, Code of Federal Regulations (21 CFR), Part 58 - Good Laboratory Practices for Nonclinical Laboratory Studies (GLPs). These findings were listed on the Form FDA-483, "Inspectional Observations" (see enclosed copy). The FDA-483 was presented to and discussed with Dr. George R. Newkome, Vice President of Research. Drs. Robert W. Engelman, Director, Comparative Biomedicine; Richard F. Walker, Director, Division of Compliance Services; and Mr. Dennis L. Freeman, Coordinator of Program Services, were also present at this discussion and received copies of the FDA-483. The following list of violations is not intended to be an all-inclusive list of deficiencies observed during the inspection:

Failure of test facility management to designate a study director before the studies were initiated and to require that personnel engaged in the conduct of nonclinical trials were knowledgeable regarding the study requirements, the GLPs, and study functions that they were to perform in accordance with 21 CFR 58.31(a) and (f), 58.29 and 58.33.

- Management failed to designate a study director before the start of the referenced nonclinical studies. For example, Dr. Angell conducted the studies without being designated as a study director who is subject to GLP requirements. For each nonclinical study, a scientist or other professional of appropriate education, training, and experience, or combination thereof, must be identified as the study director. The study director is responsible for assuring that all applicable good laboratory practice regulations are followed. The study director has the overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation and reporting of results, and represents the single point of study control.

- Further, there was no documentation available to document that management had assured that any of the other study personnel were made aware of the specific functions they were to perform for the nonclinical studies, or that they had appropriate knowledge or training in the GLP requirements applicable to personnel who conduct nonclinical laboratory studies. In fact, USF laboratory management informed the FDA investigator that USF had not been made aware that the referenced studies were for FDA submission.

Failure of test facility management to assure that there is a Quality Assurance Unit (QAU) in accordance with 21 CFR 58.31(c) and 58.35.

- The inspection revealed that prior to January, 1999, a QAU had not been assigned responsibilities for the independent monitoring of nonclinical laboratory studies to assure USF management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with the 21 CFR Part 58.

- The QAU duties that were not performed for the referenced studies include: maintenance of a master schedule sheets, maintenance of copies of approved protocols, periodic inspections of ongoing studies to identify problems that may affect study integrity, submission of written study status reports, determinations of deviations from approved protocols or standard operating procedures, review of final study reports, preparation of quality assurance statements, maintenance of records of QAU procedures, and maintenance of records of inspections in accordance with 21 CFR 58.35(a), 58.35(b)(1), (b)(2), (b)(3), (b)(4), (b)(5), (b)(6), (b)(7), and 58.35(c).

Failure to have approved written protocols that clearly indicate the objectives and methods for the conduct of the study in accordance with 21 CFR 58.120 and failure to conduct a nonclinical study in conformity with a written protocol in accordance with 21 CFR 58.130

- Neither USF nor [redacted] was able to provide a copy of a written protocol for the [redacted] studies. During the inspection the nonclinical laboratory personnel searched for protocols for the studies identified above, however, they were unable to find them or provide any copies to the FDA investigator.

- The study records that were available failed to include the informational content necessary to fulfill the requirements of a protocol in compliance with 21 CFR 58.120. The copies of "Requests for Use of Animals" that were available during the inspection failed to include all information that is required of a protocol. Among other things, the information lacking from these documents includes a complete description of experimental design and test systems, identification procedures, methods for the control of bias, all dosage levels and experimental methods, type and frequency of all tests, measurements and analyses to be performed, and proposed statistical methods.

- The available study records failed to document conformance with a protocol in accordance with 21 CFR Part 58.130. The inspection revealed that procedures documented in the LEO procedure log did not always correspond to the procedures recorded in the approved IACUC Applications for the Use of Animals in Research. For example, the application for IACUC study 1166 states that a single pulse of laser energy will be used [redacted] in the test [redacted], when hundreds of pulses were routinely administered to test animals in this study. Further, significant inconsistencies were noted between the "Request for Use of Animals" and other records documenting the procedures performed on animals with respect to surgical procedures, laser power settings, numbers of [redacted], medication regime, and postoperative care.

- The inspection revealed that animal health and observation records are inconsistent and incomplete. Required information and observations were not always recorded. Animal disposition records were not available for all animals.

Failure to maintain adequate written operating procedures and records concerning maintenance and calibration of equipment in accordance with 21 CFR 58.63(b) and (c).

There were no written operating procedures and records available concerning the testing, calibration/standardization, and maintenance of the [redacted] Lasers used during the referenced studies.

Failure to prepare an adequate and complete final report of a nonclinical laboratory study in accordance with 21 CFR 58.185.

- A final study report, signed and dated by the study director, was not available.

- FDA audited a study report that was provided by [redacted] entitiled, [redacted] (sic) STUDY IN ADULT FOX HOUNDS." This summary report was compared to the laboratory records. The inconsistencies that were observed included the following: the [redacted] report summarizes data for 32 dogs, however, the laboratory's LEO procedure log contains data for 34 dogs; the [redacted] report contains specific data points for 9 dogs that are not documented in the LEO procedure log; and, the [redacted] report indicates a power setting of 1125-8 watts for dog 14 (96-10), when the LEO log entry documents a power setting of 1225-8 watts for dog 96-10.

- Other discrepancies were noted among supporting laboratory records. For example, at least 5 inconsistencies were noted between log entries and animal care/use records for the 34 animals in the LEO procedure log. For dog 96-102, the LEO procedure log identifies the dog as female, when the care/use record identifies the dog as male.

Failure to maintain study documentation and to store material in an orderly fashion for expedient retrieval in accordance with 21 CFR 58.190.

- There were no archives for the orderly storage and retrieval of records for studies conducted prior to January 1999.

The nature and severity of these findings seriously compromises our evaluation of the reliability and integrity of data from nonclinical laboratory studies conducted at your testing facility.

We acknowledge that a limited audit of an ongoing study "**The Evaluation of the Safety and Long-term Functionality of the [redacted] Prosthesis in Canines,**" that was initiated during January 1999, showed substantial compliance with FDA regulations. However, any other research conducted in your facility prior to this date that has a potential for submission to FDA in support of research or marketing applications must be identified. **Please provide us with a listing of all nonclinical studies conducted at your facility. Additionally, you must notify each potential sponsor that their studies were not conducted in accordance with the GLP regulations and provide us with a copy of each notification.**

The GLP deficiencies observed during this inspection and data audit require corrective action. You must address these deficiencies and establish procedures to ensure that any on-going or future studies will comply with regulations. Please notify this office, in writing, within fifteen (15) working days of receipt of this letter, of the specific corrective actions you have taken, or will be taking, to address these deficiencies and to achieve compliance with FDA regulations. Once you have provided assurances that all current and future studies are in compliance, we will advise the district office of your actions and will request them to re-inspect your facility.

If corrective action cannot be completed within 15 working days, you may request an extension of the time in which to respond by stating the reason for the delay and the time within which the corrections will be completed. We will review your response and determine whether the actions are adequate. Failure to take prompt action to correct these deficiencies may result in further regulatory action including disqualification of the facility.

Please direct your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Rodney T. Allnutt. We also request that you send a copy of your response to the FDA Florida District Office, 555 Winderly Place, Suite 200, Maitland, Florida 32751.

If you have any questions concerning this matter, please contact Mr. Rodney T. Allnutt at (301) 594-4723, ext. 140.

Sincerely yours,

Michael E. Marcarelli

for Lillian J. Gill
Director
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and Radiological Health

Enclosure

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